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Abstract

Background: Using more than one psychotropic substance is accompanied with increased risks for psychiatric and physical disorders. Accordingly, deficits in basal cognitive functions have been consistently associated with polysubstance use (PSU), whereas little is known about potential impairments in more complex socio-cognitive skills, which are relevant for daily-life functioning. Therefore, we investigated the effects of toxicological validated stimulant PSU on social cognition under consideration of potential cumulative effects.

Methods: We compared socio-cognitive performances of 47 individuals with stimulant PSU with 59 matched stimulant-naïve controls using the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). Additionally, social network size was assessed by the Social Network Questionnaire (SNQ). Hair and urine testing was employed to categorize three PSU subgroups (3, 4, and ≥5 substances used) and to ensure drug abstinence in controls.

Results: Individuals with stimulant PSU showed lower emotional empathy (MET) and a smaller social network (SNQ) compared to controls (both with linear trends for increasing number of used substances: $p<.05$). In contrast, cognitive empathy (MET and MASC) was largely unaffected by PSU. Additional linear regression analyses within PSU individuals revealed number of used substances as the best predictor for inferior performance in emotional empathy ($p<.01$), while severity of the use of single substances or substance-classes did not show a significant impact.

Conclusion: These findings demonstrate cumulative adverse effects of stimulant PSU on an important facet of socio-cognitive functioning. Therefore, emotional empathy deficits should be targeted in future interventions and rehabilitations for individuals with PSU.

Keywords: poly drug use, stimulants, empathy, Theory-of-Mind, emotion recognition, emotion perception

1. Introduction

The use of more than one psychotropic substance, concurrently or consecutively, is termed polysubstance use (PSU) (EMCDDA, 2002; Meyerhoff, 2017). PSU was previously diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) by the use of at least three substances (excluding caffeine and nicotine) within the same 12-month period. However, this definition has recently been removed in the DSM-5 (American Psychiaric Association, 1994; American Psychiatric Association, 2013).

Three main reasons for PSU are commonly reported: (1) it can induce cumulative or complementary effects, (2) it can compensate negative effects of other drugs, and (3) it can reflect the replacement of a drug by another drug due to low prices, availability, or fashion (EMCDDA, 2009; Preedy, 2016). While the frequency of monosubstance use is decreasing over the last years, PSU instead has become a serious and increasing public health concern with regard to psychological (e.g., depression or anxiety) and physiological illnesses accompanied by an increased risk of intoxication, injury, and death (Connor et al., 2014; Karjalainen et al., 2017; Martin, 2008). Accordingly, 38% of drug-related hospital emergency presentations in Europe were reported to be caused by PSU (EMCDDA, 2016).

Recently, neurocognitive effects of PSU have been investigated intensively indicating an increased interest in this research field of substance use. The study by Schmidt et al. (2017) investigated neurocognitive functioning in individuals with PSU and alcohol use disorders (AUD). The PSU group revealed inferior performances in auditory-verbal memory and learning, inhibitory control of impulsivity, decision-making, and global cognition compared to AUD (Schmidt et al., 2017). This is in line with previous findings of behavioral and neuroimaging studies investigating cognition in individuals with PSU and reporting similar deficits in cognitive efficiency, attention, memory, and delayed discounting (Connor et al., 2014; Fernandez-Serrano et al., 2011; Moody et al., 2016; Pennington et al., 2015).

Apart from consistently reported neurocognitive impairments of PSU, little is known about its socio-cognitive sequelae. Social cognition includes prosocial and interpersonal behavior such as empathy and emotion recognition, which are crucial for daily-life interactions (Singer and Lamm, 2009; Walter,

2012). Empathy is a multidimensional construct subdivided in at least two components: 1) cognitive empathy is characterized by the ability to understand the feelings of others without necessarily experiencing them and involves perspective-taking, also called *Theory-of-Mind* (ToM), and emotion recognition; 2) emotional empathy means to subjectively experience the others' feelings (Decety and Jackson, 2004; Eres et al., 2015; Walter, 2012). Deficits in empathy have been demonstrated in various psychiatric diseases such as autism (Blair, 2005; Dziobek et al., 2008), schizophrenia (Derntl et al., 2009), depression (Cusi et al., 2011), psychopathy (Blair, 2005; Pfabigan et al., 2015), and in individuals with substance use disorders (Quednow, 2017; Reay et al., 2006; Uekermann and Daum, 2008). More specifically, alcohol dependence is associated with deficits in emotional empathy, emotion recognition, and humor processing (Kornreich et al., 2003; Maurage et al., 2015; Maurage et al., 2011; Mohagheghi et al., 2015; Uekermann et al., 2007). Studies with chronic methamphetamine users consistently demonstrated deficits in emotion recognition and ToM (Henry et al., 2009; Kim et al., 2011). Furthermore, previous studies of our group revealed deficits in emotion recognition, ToM, and emotional empathy in cocaine users, whereas non-medical methylphenidate users mainly showed impairments in cognitive empathy (Hulka et al., 2013; Maier et al., 2015; Preller et al., 2014). In contrast, chronic 3,4-methylenedioxymethamphetamine (MDMA) users showed superior cognitive empathy accompanied by unaffected emotional empathy (Wunderli et al., 2017b). Studies investigating opioid-related effects reported impairments in social perception in substituted patients (Kornreich et al., 2003; McDonald et al., 2013). Finally, neuroimaging and electrophysiological studies with chronic cannabis users revealed altered physiological response during task performances of ToM and empathy (Platt et al., 2010; Roser et al., 2012; Troup et al., 2016).

Although PSU is clinically highly relevant, studies investigating social cognition in individuals with PSU are limited to date. The study by Ferrari et al. (2014) demonstrated reduced emotional empathy with preserved cognitive empathy in addicted PSU patients compared to controls using a subjective self-rating scale of the empathy quotient . These effects were specifically pronounced for males with PSU. Furthermore, deficits in recognition of facial emotion expressions were reported for individuals with PSU using a computer-based Ekman Faces Test (Fernandez-Serrano et al., 2010; Verdejo-Garcia et al.,

2007). Moreover, a recent neuroimaging review by Meyerhoff (2017) reported consistent findings in individuals with PSU regarding structural alterations in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), which are associated with ToM and empathy (Abu-Akel and Shamay-Tsoory, 2011; Bernhardt and Singer, 2012; Fan et al., 2011).

In sum, studies investigating socio-cognitive functioning in individuals with PSU mainly focused on emotion recognition or subjective self-rating scales for empathy. Therefore, our aim was to assess emotional and cognitive empathy with complex stimuli in situational contexts using performance tasks. Furthermore, only two-group analyses were conducted so far comparing polysubstance users with controls while disregarding cumulative effects of multiple substances. Based on the study by Witt et al. (2015) reporting decreased cognitive performance with an increased number of consumed antiepileptics, we created a 4-group design for our study (three PSU subgroups vs. healthy controls) in order to consider the number of used substances. Although studies investigating PSU differ with respect to their classifications, they all have in common that PSU was assessed by self-reports. Because it is well-known that self-reports in substance users are distorted by social desirability biases and memory alterations (Latkin et al., 2017; Magura and Kang, 1996; Quednow et al., 2006), a further innovative aspect of our study was to investigate an objectively validated PSU sample based on hair and urine toxicology analyses. Given that deficits of emotional empathy have been shown for a variety of single substance users as well as for PSU assessed only by self-reports, we hypothesized that an increased number of used substances goes along with decreased performances in emotional empathy accompanied by increased impairments in real-life social functioning reflected in a smaller social network size.

2. Methods

2.1. Recruitment and participants

Participants in our PSU and control groups were initially recruited and assessed for our previous cocaine (Zurich Cocaine Cognition Study, ZuCoSt[2]; Hulka, Preller, Vonmoos, et al., 2013; Preller, Hulka, Vonmoos, et al., 2014; Vonmoos, Hulka, Preller, et al., 2013) and MDMA studies (Wunderli et al., 2017a). The present PSU sample was composed of individuals who were excluded from these previous studies because of PSU. Participants were initially recruited through flyers in addiction centers and hospitals, advertisements in local newspapers, internet platforms, and word of mouth. All participants were tested at the Psychiatric Hospital of the University of Zurich, aged between 18 and 60 years, had proficiency in German language, and showed no severe physical, neurological, and psychiatric disorders according to DSM-IV with exception of substance abuse/dependence, attention deficit hyperactivity disorder (ADHD), and history of depression for the PSU sample. Specific exclusion criteria for the control group were a positive urine or hair toxicology and a medium to high alcohol risk level (see 2.2.). All participants were asked to abstain from illegal substances for at least 72 hours and from alcohol 24 hours prior to the measurement. The study was approved by the Ethic Committee of the Canton Zurich. All participants provided written informed consent and were compensated for their participation.

2.2. PSU sample

Referring to DSM-IV criteria, we defined PSU as the consumption of at least three psychotropic substances within the last six months, including alcohol as the only legal drug and excluding tobacco use. Objective data were used to get a precise and valid estimation of illegal drug use and to avoid social desirability in subjective questionnaires. According to the social desirability hypothesis, Harrison (1997) postulated that the validity of self-reported substance use decreases in relation to the increase in stigmatization of the substance that is used. Alcohol is a legal drug, which is socially recognized with low stigmatization compared to illegal substances. Therefore, alcohol was the only drug for which no objective validation was collected, as we believed that our subjective data of

alcohol use were less biased than illegal drug use (Del Boca and Darkes, 2003; Lintonen et al., 2004). Based on the World Health Organization (WHO, 2000), we defined three groups of alcoholic risk consumption levels for men and women respectively with low (1), medium (2), and high (3) risk alcohol consumption levels (Table S1a[1]). Low level of alcohol consumption was not considered for the number of used substances in the PSU subgroups. Chronic cannabis use was confirmed by urine analyses because participants were asked to abstain from illegal substances for at least 72 hours and the window of detection for THC in urine samples is up to more than three weeks in frequent cannabis users (Musshoff and Madea, 2006). Additional psychotropic substance use (e.g., cocaine, MDMA, amphetamines, opioids, ketamine, 2,5-dimethoxy-4-bromophenethylamine [2C-B]) was quantified by hair analyses (see also 2.4. below). For urine samples, delta-9-tetrahydrocannabinol (THC) concentrations of at least 50 ng/ml were considered positive (Methods S1[1]). Three equal groups in relation to the group size were calculated over all positive urine samples of initially recruited participants (n=60) to differentiate again between low (1), medium (2), and high (3) substance use (Table S1b[1]). The same procedure was performed with hair samples to differentiate between three levels of substance use severity for each illegal substance (see Methods S2[1] & Table S1c[1]). The average of the normalized cocaine, MDMA, and amphetamine hair values was used to define the final cut-off values for low (1), medium (2), and severe (3) substance use (Table S1c[1]). Furthermore, a PSU severity index (PSUSI) over all substances was calculated by summarizing the severity levels low (1), medium (2), high (3) of used substances.

Because participants were initially recruited for our previous studies investigating cocaine and MDMA users, participants were excluded if they revealed consumption of less than three substances or high severity level (level 3) of only one single substance accompanied with low levels (level 1) of additional substances indicating a primary drug of choice. Our final sample comprised three subgroups of PSU using three (n=31), four (n=10), and five or more substances (n=6) and 59 controls (Fig. 1). The groups were carefully matched for age, verbal IQ, years of education, and tobacco use.

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:

Data from the healthy stimulant-naïve controls of the present study has already been published in previous papers including the ZuCoSt^2 and MDMA study (Vonmoos et al., 2013; Wunderli et al., 2017a). However, our PSU sample does not contain any cocaine user included in previous ZuCo^{2}St publications (e.g., Vonmoos et al., 2013) but revealed an overlap of 42.6% with the MDMA polydrug sample reported in the study by Wunderli et al. (2017a).

2.3. Clinical Assessment

The Structured Clinical Interview for Axis-I DSM-IV disorders (SCID I) was conducted by trained psychologists. Furthermore, participants completed the DSM-IV self-rating questionnaire assessing Axis-II personality disorders (SCID II). Because cocaine use was previously associated with higher scores in antisocial and narcissistic personality disorder (PD) domains (Preller et al., 2014), Cluster B PD including antisocial, borderline, histrionic, and narcissistic PD was calculated. To control for potential mood or attention differences between groups, the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Attention Deficit Hyperactivity Disorder (ADHD) self-rating scale (ADHD-SR) (Rösler et al., 2005) were conducted. Premorbid verbal IQ was estimated by the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 1999), which is a standardized German vocabulary test.

2.4. Substance assessment

Substance use over the last six months was assessed by means of a structured and standardized interview for psychotropic drug consumption (Quednow et al., 2004). Additionally, illegal substance use over the last six months was examined by 6cm-hair samples, which were segmented into two 3cm segments analyzed separately. The average concentration of both hair segments was calculated and used for the final analyses. Twenty individuals (34%) in the control group and 13 (28%) in the PSU group had only one hair segment due to insufficient hair length. In these cases only this single values were introduced in the analyses. Hair samples were taken from the posterior vertex region of the head to assess the concentration of 11 common drugs and their metabolites by liquid chromatography-tandem mass spectroscopy (LC-MS/MS). Additionally, urine analyses were

conducted by semi-quantitative enzyme multiplied immunoassays in order to assess cannabis use (see also Methods S1[2]).

2.5. Socio-cognitive assessment

2.5.1 MASC

The Movie for Assessment of Social Cognition (MASC) is a 15-minute video-based task with the intention of assessing mental and emotional perspective-taking (ToM), which is a facet of cognitive empathy, with an ecological valid method (Dziobek et al., 2006). During the video, participants were asked about the characters' feelings, thoughts, and intentions. Four response alternatives were presented with one correct answer and three distractors.

2.5.2 MET

The Multifaceted Empathy Test (MET) is a computer-based task comprising 40 pictures showing people in distinct positive and negative emotional situations (Dziobek et al., 2008). Based on the multidimensional construct of empathy, the MET distinguishes between emotional and cognitive empathy. Emotional empathy (EE) is subdivided into explicit emotional empathy (EEE) assessed by ratings of the participants' empathic concern, and implicit emotional empathy (IEE) measured by ratings of the participants' arousal on a 9-point Likert scale. Cognitive empathy (CE) was measured by presenting four response-alternatives from which the participant had to choose one emotion, which fits the best to the person's mental state on the picture.

Additionally, we constructed a global cognitive empathy domain score (CES) including z-transformed CE and MASC data based on means and standard deviations of the control group according to Wunderli et al. (2017b).

[2] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: 10.1016/j.drugalcdep.2018.06.001

2.5.3 SNQ

Furthermore, participants' social contacts were measured by the Social Network Size Questionnaire (SNQ, for details see Preller et al., 2014). The number of personal contacts during the previous four weeks in specific life areas (household, family, work or education, friends, neighbors, and others) were named and subsumed to the total network size.

2.6. Statistical analysis

Statistical analyses were performed by SPSS 23.0 for Mac. Frequency data were analyzed by means of Pearson's χ^2 test. To determine quantitative differences between groups, analyses of variance (ANOVA) and covariance (ANCOVA) with the four groups as fixed factor (three PSU subgroups and controls) were used to control for age and sex because of differences in sex distribution between our groups and associations with prosocial behavior (Beadle et al., 2015; Kret and De Gelder, 2012; Miller et al., 1991). Furthermore, the severity index of PSU (PSUSI) was introduced as an additional covariate for the MET and MASC due to differences of the PSUSI between the groups and because of putative association between severity of substance use and emotion recognition in individuals with PSU (Fernandez-Serrano et al., 2010). Sidak-corrected post hoc analyses and linear group contrasts for trend analysis were performed regarding the number of used substances. Multiple linear regression analyses (forced entry) were conducted to estimate potential single substance-class effects (alcohol, THC, stimulants, and empathogens, see 3.3.) on socio-cognitive functioning over all individuals with PSU (n=47). Further linear regression analyses within the PSU subgroups were used to determine potential associations of clinical and demographic variables on socio-cognitive functioning. Cohen's *d* effect sizes were calculated by the means and pooled standard deviations of the four groups (Cohen, 1988). The confirmatory statistical comparisons were carried out on a significance level of $p<.05$ (two-tailed).

3. Results

3.1. Demographic characteristics

Because of our matching procedure, groups did not differ with regard to verbal IQ, years of education, age, and smoking behavior (Table 1). However, individuals using five or more substances showed a different sex distribution compared to the other PSU subgroups with more females than males in this group. Individuals with PSU scored higher than controls on the BDI and ADHD-SR sum scores as substance use disorder is commonly associated with depression and ADHD (Quello et al., 2005; Zulauf et al., 2014). Furthermore, Cluster B PD was significantly higher in polysubstance users (p<.001) compared to controls but no linear trend was detectable (p=.158). Means of alcohol consumption in gram and substance concentrations in hair and urine samples are shown in Table 1. The distribution of substance use between PSU subgroups are shown in Figure 3. The most frequently used substances over all PSU subgroups were cocaine (83%), MDMA (76.6%), alcohol (57.4% moderate or high use, Figure S1a[3]), amphetamine (40.4%), and cannabis (36.2%; Figure S1b[3]). The most common substance combinations over all PSU subgroups were cocaine-MDMA-alcohol (29.8%) and cocaine-MDMA-amphetamine (25.5%). As intended, the control group showed only low levels of alcohol consumption and no objectively quantified illegal substance use.

3.2. Socio-cognitive functioning

3.2.1. MASC

An ANCOVA corrected for age, sex, and PSUSI with the dependent variable ToM correct sum score revealed no differences between the four groups and no linear trend (Table 2). Additional linear regression analysis including demographic and clinical variables as predictors revealed age (β=-.39, t=-2.39, p<.05) as the only significant predictor for ToM performances (Table S2a[3]).

3.2.2. MET & CES

[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:

ANCOVAs were performed for the dependent variables CE, EE, EEE, IEE, and CES with the fixed factor groups (Table 2). The results revealed differences between groups in EE (p<.05) with a significant linear trend (p<.05) showing decreased empathy scores with an increased number of used substances (Figure 2). No differences were found for CE and the global cognitive empathy score CES. Sidak-corrected pairwise comparison for emotional empathy revealed significant differences between individuals using three and four and three and five substances (Table 2). Cohen's *d* yielded substantial differences in EEE, IEE, and EE mainly for individuals using more than three substances compared to controls and compared to individuals using three substances (Figure 4). Additional linear regression models revealed no significant demographic predictors for EE and CES (Table S2b[4] & S2c[4]).

3.2.3. Social Network

ANCOVA corrected for sex and age was conducted for analyzing differences of social contacts between the four groups. Results revealed a significant group effect and a linear trend (p<.05) with the smallest social network size in individuals using five or more substances (Table 2). Although Sidak-corrected pairwise comparisons revealed no significant differences between groups, the effect size between individuals using five or more substances and controls was very large (d=1.01) regarding social network size (Figure 4). Given that the reduced network sizes of the PSU groups might have been biased by unemployment status (i.e., less social contacts in work-related areas), we conducted an additional ANCOVA with employment status as a covariate. However, the main effects remained significant even after controlling for the employment status (group: F(1,98)=2.89, p=.039, linear contrast: p=.034). Furthermore, linear regression analysis including demographic and clinical variables as predictors revealed age as the only significant predictor (β=-.36, t=-2.07, p<.05) for social network size (Table S2d[4]).

[4] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:

3.3. Regression models

In order to find potential substance-class predictors for socio-cognitive functioning, we used multiple regression models (forced entry) within the PSU group (n=47, Table S3[5]). Model 1 concerned the estimation for the effects of single substance-class parameters, number of used substances, and PSUSI on EE. In the first step, dummy coded variables with the most frequently used substances separated for their neurochemical classes were included to estimate the effects of single substances independently. Therefore, we built four dummy coded substance-classes of alcohol use (n=27), THC use (n=17), stimulant use (n=45; cocaine, amphetamine, methamphetamine, and methylphenidate), and empathogen use (n=36, MDMA and 2C-B). Due to an insufficient number of ketamine (n=6) and opioid (n=4) users, we did not include these substances in the model. In a second step, we additionally introduced the number of used substance and in a third step the variable PSUSI. The analysis revealed no significance for any substance-class parameter (Table S3[5]). The number of used substances was the only significant predictor for EE (β=-.47, t=-3.04, p<.01; Model 1). Analogously, the same regression analysis was conducted with the dependent variable SNQ (Model 2). The dummy coded THC substance-class revealed statistical significance for social network size (β=.33, t=2.08, p<.05) showing more social contacts (M=19.12, SD=6.6) than stimulant (M=16.33, SD=6.8), empathogen (M=16.61, SD=6.6), and alcohol users (M=16.44, SD=7.3).

[5] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:

4. Discussion

The innovative purpose of this study was to investigate socio-cognitive functioning in objectively validated stimulant polysubstance users and considering the number of used substances as well as severity of PSU. Our results revealed decreased performance in emotional empathy and fewer social contacts with an increased number of used substances. However, cognitive empathy was largely unaffected by PSU. Additionally, neither overall severity of PSU (PSUSI) nor single substance-classes revealed an impact on emotional empathy. In sum, these results indicate that individuals with PSU show distinct deficits in socio-cognitive functioning, which are worsening with the number of used substances.

Our results with regard to the performance task MET are consistent with the study by Ferrari et al. (2014) demonstrating self-reported deficits in emotional empathy but not in cognitive empathy in individuals with PSU. Furthermore, the authors reported sex differences revealing deficits of cognitive empathy only in women and stronger deficits of emotional empathy and the total empathy score in men. However, our statistical analyses did not detect a significant interaction of sex and PSU on EE. The present results are also in accordance with previous neuroimaging findings in individuals with PSU reporting grey matter atrophy found in regions associated with emotional empathy such as the ACC (Fan et al., 2011), while no structural differences between individuals with PSU and alcohol users were reported (Meyerhoff, 2017). We found similar deficits in emotional empathy related to stimulant PSU as shown for alcohol dependent individuals (Maurage et al., 2011; Mohagheghi et al., 2015) and also for pure cocaine users (Preller et al., 2014). Furthermore, the global cognitive empathy score (CES) remained unaffected by PSU. Therefore, we could not replicate the findings by Fernandez-Serrano et al. (2010) and Verdejo-Garcia et al. (2007), reporting deficits in emotion recognition, which is one important facet of cognitive empathy. However, crucial differences compared to our study sample exist. First, their PSU group was defined by self-reports, whereas our sample was objectively validated by hair and urine toxicology because self-reported substance use is often biased by distorted memories or social desirability (Harrison, 1997; Latkin et al., 2017; Magura and Kang, 1996; Quednow et al., 2006). Secondly, only two-group comparisons were conducted

disregarding the number of used substances. Moreover, Fernandez-Serrano et al. (2010) and Verdejo-Garcia et al. (2007) used the Ekman Faces Test assessing only emotion recognition in faces, whereas the MET used in our study measures emotion recognition in complex emotionally laden scenes likely engaging processes integrating different pathways of emotion recognition. Finally, our PSU group showed much less opioid consumption compared to the other study samples because opioid use was an exclusion criterion in the previous studies from which we created our PSU group.

Given that we created the PSU sample out of excluded participants initially recruited for cocaine or MDMA use, we additionally analyzed the effects of stimulants, empathogens, THC, and alcohol on socio-cognitive functioning. However, no single substance-class indicator was identified for EE and CES. One possible reason for this could be that impairments in individuals with PSU rather resulted from opposing effects of different substances than from one single substance. Accordingly, findings of our previous studies using also the MET and MASC revealed deficits of emotional and cognitive empathy in relatively pure cocaine users, whereas MDMA use was associated with superior cognitive empathy (Preller et al., 2014; Wunderli et al., 2017b). Although we excluded individuals showing one primary drug, cocaine and MDMA were the most frequently used substances and the most common combination in our PSU sample. Therefore, our findings might result from the opposing effect of both substances and additional substance use. Furthermore, individuals showing more deficits in sharing other's feelings might be prone to use more substances, which leads to the discussion of the cause-effect relationship.

Although severity of substance use in individuals with PSU was discussed as a potential predictor for emotion recognition deficits in the study by Fernandez-Serrano et al. (2010), our severity index of PSU (PSUSI) revealed no association with socio-cognitive functioning. However, the authors reported that specifically lifetime quantity of cocaine use was associated with socio-cognitive deficits, which was assessed by self-reports. In contrast, the PSUSI of our study was an estimation of severity of use over all substances. Therefore, our results might indicate that reported deficits of PSU were rather driven by the number of used substances than by the summed severity of use of all substances.

Our findings demonstrate that individuals using five or more substances revealed the fewest social contacts. Moreover, cannabis users showed a larger social network than stimulant, empathogen, and moderate to heavy alcohol users. Again, this finding could be discussed by a cause-effect relationship regarding PSU and deficits in emotional empathy. Chronic PSU might induce impairments in experiencing other's feelings resulting in blunted emotional responses in given situations, which could lead to increased interpersonal conflicts and therefore to decreased social contacts. Moreover, decreased social contacts might be compensated by an increased use of additional substances. Alternatively, deficits in emotional empathy might reflect a predispositional trait (e.g., an antisocial or psychopathic personality) causing both, a decreased social network and PSU. Analysis of the SCID-II Cluster B revealed higher scores for individuals with PSU without a linear trend indicating a general antisocial and psychopathic behavior in substance users independently from the number of used substances. Similar results were also found in pure cocaine users (Preller et al., 2014). Furthermore, individuals with psychopathic PD showed similar deficits in emotional empathy as in our PSU sample (Blair, 2005) suggesting that PSU might facilitate psychopathic behavior or that individuals with psychopathic traits might tend to show PSU.

Our results indicate that individuals with PSU show preserved cognitive empathy suggesting that the ability of interpreting and recognizing emotions of others' as well as mentalizing behaviors were largely unaffected by PSU. However, the ability of subjectively sharing others' emotions was impaired in the PSU subgroups compared to controls, which is important for building meaningful interpersonal relationships and prosocial behavior (Singer and Lamm, 2009). Impaired emotional empathy can lead to severe deficits in daily life interactions especially in social relationships. Therefore, our results indicate a stronger implication of emotional empathy in the intervention and rehabilitation of PSU. Improving emotional empathy in specific intervention programs could ameliorate interpersonal communication in daily life situations and within social relationships but also during psychotherapy. Accordingly, individuals with PSU would receive a broader support of their social network, which in turn prevents relapse and facilitate a positive therapy outcome (Atadokht et al., 2015; Ellis et al., 2004; Havassy et al., 1991).

This study shows some limitations. First, our PSU sample was dominated by individuals using stimulants whereas opioid use was less present compared to other PSU studies (Fernandez-Serrano et al., 2010; Ferrari et al., 2014; Verdejo-Garcia et al., 2007). This is based on the fact that we created the sample out of former excluded participants from the ZuCoSt^2 and MDMA study where opioid use was and exclusion criterion (Hulka et al., 2013; Preller et al., 2014; Vonmoos et al., 2013; Wunderli et al., 2017a). Additionally, we could not include opioids and ketamine as dummy coded variables in the regression model due to small sample sizes. Furthermore, we were not able to use hair concentration as a variable in our regression model because they were not normally distributed even after log-transformation. Therefore, the substance-use variables were dichotomized. Secondly, the sample size for the groups using four or five substances was relatively small. Therefore, post-hoc tests mostly did not reveal significant differences between PSU subgroups. However, effect sizes showed considerable differences in social contacts and emotional empathy for the subgroups. Third, pre-existing differences and predispositions cannot be fully excluded due to our cross-sectional design. As mentioned before, no final cause statement can be done. Future studies should address this limitation conducting longitudinal studies with PSU and adding more specific instruments for psychopathic or antisocial personality traits.

Taken together, our findings indicate that individuals with stimulant PSU show discrete impairments in emotional empathy with unaffected cognitive empathy. The innovative aspect of the present study was to investigate socio-cognitive functioning in an objectively validated PSU sample and to assess cumulative effects by the number of used substances. Our results indicate a gradual decrease of social contacts and performances in emotional empathy related to an increased number of used substances. However, the ability of emotion recognition, metalizing behavior, and perspective-taking was preserved. Taken together, our results suggest a stronger focus on emotional empathy in psychotherapeutic settings for future interventions and rehabilitations in PSU.

Table 1: Demographic, clinical, and substance use data (means and standard deviations)

	Controls (n=59)	**3 substances** (n=31)	**4 substances** (n=10)	**5 substances** (n=6)	**value**	***df***	***p***
Female/male	16/43	6/25	4/6	5/1	$\chi^2 = 10.64$	3	**0.014**
Age	30.98 (9.3)	29.90 (8.9)	29.6 (7.6)	24.33 (4.0)	F = 1.05	3, 102	0.372
Years of education	10.51 (1.8)	10.32 (1.7)	10.10 (1.7)	11.00 (1.7)	F = 0.41	3, 102	0.744
Verbal IQ	105.34 (10.0)	103.03 (11.5)	104.9 (12.5)	100.83 (5.9)	F = 0.57	3, 102	0.637
Employment yes/no	50/9	23/8	8/2	4/2	$\chi^2 = 2.16$	3	0.539
BDI sum score	3.66 (4.0)	7.39 (5.5)*	7.8 (10.2)	10.17 (11.3)	F = 4.91	3, 102	**0.003**
ADHD-SR	6.36 (4.2)	15.10 (9.3)**	12.2 (6.1)	15.5 (16.4)*	F = 11.61	3, 102	**<0.001**
SCID II							
Cluster B	18.35 (12.6)	30.80 (15.1)**	31.09 (9.8)*	26.72 (16.3)	F = 7.06	3,100	**<0.001**
Smoker y/n	44/15	28/3	9/1	6/0	$\chi^2 = 5.43$	3	0.143
Cigarettes/week (only smokers)	73.24 (64.7)	93.08 (67.4)	138.44 (75.5)*	92.38 (30.9)	F = 2.61	3, 83	0.057
Alcohol g/week[a]	76.88 (59.8)	260.38 (263.3)**	298.10 (102.0)**	234.67 (145.9)	F = 19.25[b]	3, 15.4	**<0.001**
PSUSI	0.97 (0.2)	6.55 (1.4)**$^{++\wedge\wedge}$	8.20 (1.1)**$^{\circ\circ\wedge\wedge}$	10.33 (1.4)**$^{\circ\circ++}$	F = 465.58	3, 102	**<0.001**
Alcohol							
Medium-high[c] (%)	0(0%)	15 (48.4%)	8 (80%)	4 (66.7%)			
Gram/week		426.52 (292.8)	311.08 (110.0)	295.00 (143.1)			
THC							
HP pos (%)	0(0%)	12 (38.7%)	3 (30%)	2 (33.3%)			
UP ng/ml (50)[d]	0.0	117.58 (126.8)	99.00 (33.8)	218.50 (188.8)			
Cocaine							
HP pos (%)	0(0%)	25 (80.6%)	8 (80%)	6 (100%)			
HP ng/mg (0.5)[d]	0.0	7.45 (8.12)	22.08 (44.3)	9.29 (13.7)			
MDMA							
HP pos (%)	0(0%)	22 (71%)	8 (80%)	6 (100%)			
HP ng/mg (0.2)[d]	0.0	6.46 (11.6)	4.23 (7.1)	8.12 (12.3)			
Amphetamine							
HP pos (%)	0(0%)	7 (22.6%)	7 (70%)	5 (83.3%)			
HP ng/mg (0.2)[d]	0.0	0.58 (0.6)	0.79 (0.6)	5.73 (6.9)			
Methamphetamine							
HP pos (%)	0(0%)	0 (0%)	1 (10%)	1 (16.7%)			
HP ng/mg (0.2)[d]	0.0	0.0	0.73 (0.0)	0.49 (0.0)			
Methylphenidate							
HP pos (%)	0(0%)	6 (19.4%)	1 (10%)	0 (0%)			
HP ng/mg (0.02)[d]	0.0	0.12 (0.1)	0.07 (0.0)	0.0			
Ketamine							
HP pos (%)	0(0%)	2 (6.5%)	1 (10%)	3 (50%)			
HP ng/mg (0.1)[d]	0.0	0.42 (0.1)	0.38 (0.0)	0.35 (0.4)			
2C-B							
HP pos (%)	0(0%)	1 (3.2%)	1 (10%)	1 (16.7%)			
HP ng/mg (0.1)[d]	0.0	0.09 (0.0)	0.11 (0.0)	0.13 (0.0)			
Morphine							
HP pos (%)	0(0%)	0 (0%)	1 (10%)	1 (16.7%)			
HP ng/mg (0.2)[d]	0.0	0.0	0.20 (0.0)	1.75 (0.0)			
Codeine							

HP pos (%)	0(0%)	0 (0%)	1 (10%)	1 (16.7%)
HP ng/mg (0.2)[d]	0.0	0.0	0.93 (0.0)	0.55 (0.0)
Tramadol				
HP pos (%)	0(0%)	2 (6.5%)	0 (0%)	0 (0%)
HP ng/mg (0.2)[d]	0.0	4.68 (6.1)	0.0	0.0
Methadone				
HP pos (%)	0(0%)	1 (3.2%)	0 (0%)	0 (0%)
HP ng/mg (0.2)[d]	0.0	1.15 (0.0)	0.0	0.0

Note. ANOVAs and Chi^2 for frequency distribution (two-tailed). Significant p-values (p<.05) are shown in bold.
Data for Cluster B PD was missing for two participants of the control group. Substance data reported for participants with positive substance values.
* Indicates Sidak post hoc *p*<.05 vs. controls, ** *p*<.01 vs controls. ° Indicates Sidak post hoc *p*<.05 vs. 3 substances used, °° *p*<.01 vs. 3 substances used. [+] Indicates Sidak post hoc *p*<.05 vs. 4 substances used, [++]*p*<.01 vs. 4 substances used.
[^]Indicates Sidak post hoc *p*<.05 vs. 5 substances used, [^^] *p*<.01 vs. 5 substances used.
ADHD: attention-deficit/hyperactivity disorder, BDI: Beck's Depression Inventory, PSUSI: polysubstance use severity index
[a] Alcohol use over all participants
[b] Welch test
[c] WHO definition (2000)
[d] Cut-off values

Table 2: Results of socio-cognitive functioning (mean and SE)

	controls (n= 59)	**3 substances** (n=31)	**4 substances** (n=10)	**5 substances** (n=6)	***F***	***df, df***	***p***	***p linear contrast***
MASC[a]								
ToM sum correct	34.25 (1.5)	32.53 (1.5)	34.66 (2.5)	31.10 (3.7)	1.02	3, 99	0.385	0.648
MET[a]								
Cognitive empathy CE	24.10 (1.4)	24.58 (1.4)	25.82 (2.4)	25.43 (3.5)	0.19	3, 99	0.905	0.722
Emotional empathy EE	5.42 (0.5)	4.86 (0.5)	3.30 (0.8)*	2.60 (1.2)	3.64	3, 99	**0.015**	**0.049**
EEE	5.61 (0.5)	5.13 (0.5)	3.38 (0.8)*	2.80 (1.1)*	4.58	3, 99	**0.005**	**0.040**
IEE	5.23 (0.5)	4.60 (0.5)	3.22 (0.8)	2.40 (1.3)	2.68	3, 99	0.051	0.068
CES[a]								
Global CE score	0.02 (0.2)	-0.09 (0.3)	0.28 (0.4)	-0.13 (0.6)	0.70	3, 99	0.556	0.973
SNQ[b]								
Social contacts	19.75 (0.8)	16.70 (1.1)	17.17 (1.9)	13.17 (2.6)	3.13	3, 99	**0.029**	**0.029**

Note. ANCOVAs corrected for age, sex, and [a]PSUSI.
[b] Data for one participant of the control group was missing.
* Indicates Sidak post hoc *p*<.05 vs. 3 substances used.
EEE: explicit emotional empathy, IEE: implicit emotional empathy, PSUSI: polysubstance use severity index, SNQ: social network questionnaire, ToM: theory of mind

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Highlights (3-5 highlights; max 85 characters including spaces per bullet point)

- Investigation of cumulative effects of polysubstance use on socio-cognitive function.
- Objectively validated group classification defined by hair and urine toxicology.
- Decreased emotional empathy was associated with increased number of used substances.
- Increased number of used substances was accompanied with fewer social contacts.
- Deficits were not associated with single substance-classes or severity of substance use.

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Figure Caption

Fig. 1. Flow diagram of the final study sample.

Note. Hair samples (HS), polysubstance use (PSU), urine samples (US), years of education (YoE).

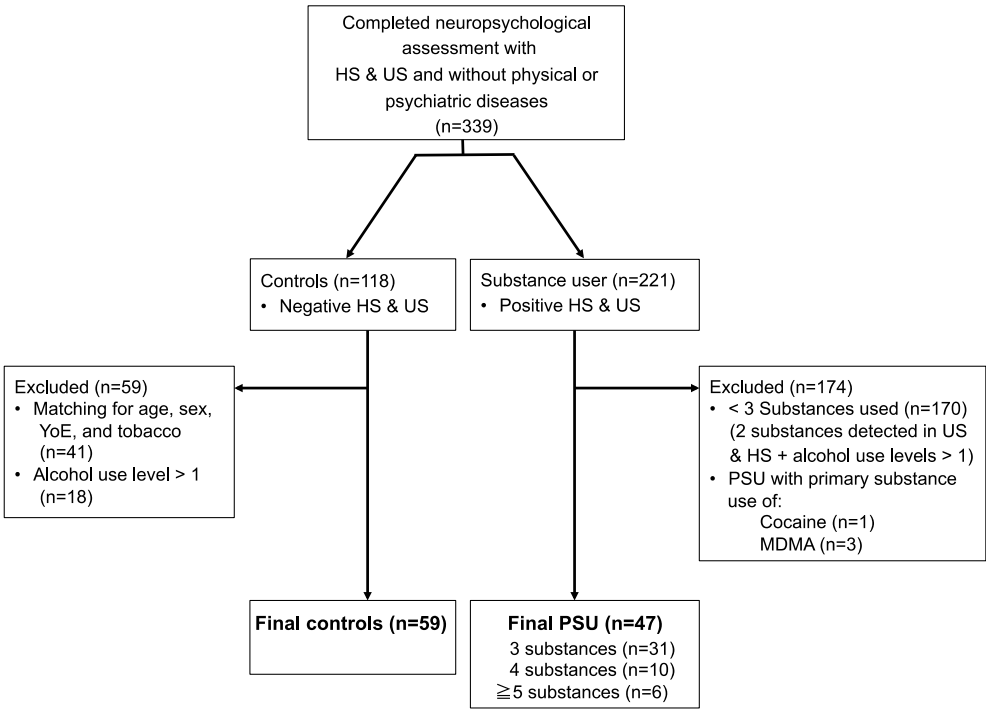

Completed neuropsychological assessment with HS & US and without physical or psychiatric diseases (n=339)
Controls (n=118)
• Negative HS & US
Substance user (n=221)
• Positive HS & US
Excluded (n=59)
• Matching for age, sex, YoE, and tobacco (n=41)
• Alcohol use level > 1 (n=18)
Excluded (n=174)
• < 3 Substances used (n=170) (2 substances detected in US & HS + alcohol use levels > 1)
• PSU with primary substance use of:
Cocaine (n=1)
MDMA (n=3)
Final controls (n=59)
Final PSU (n=47)
3 substances (n=31)
4 substances (n=10)
≧5 substances (n=6)

Figure Caption

Fig. 2. Means and standard errors of emotional empathy (EE) and its subscales explicit emotion empathy (EEE) and implicit emotional empathy (IEE) of the MET.

Note. Corrected for age, sex, and PSUSI. * Indicates Sidak post hoc $p<.05$.

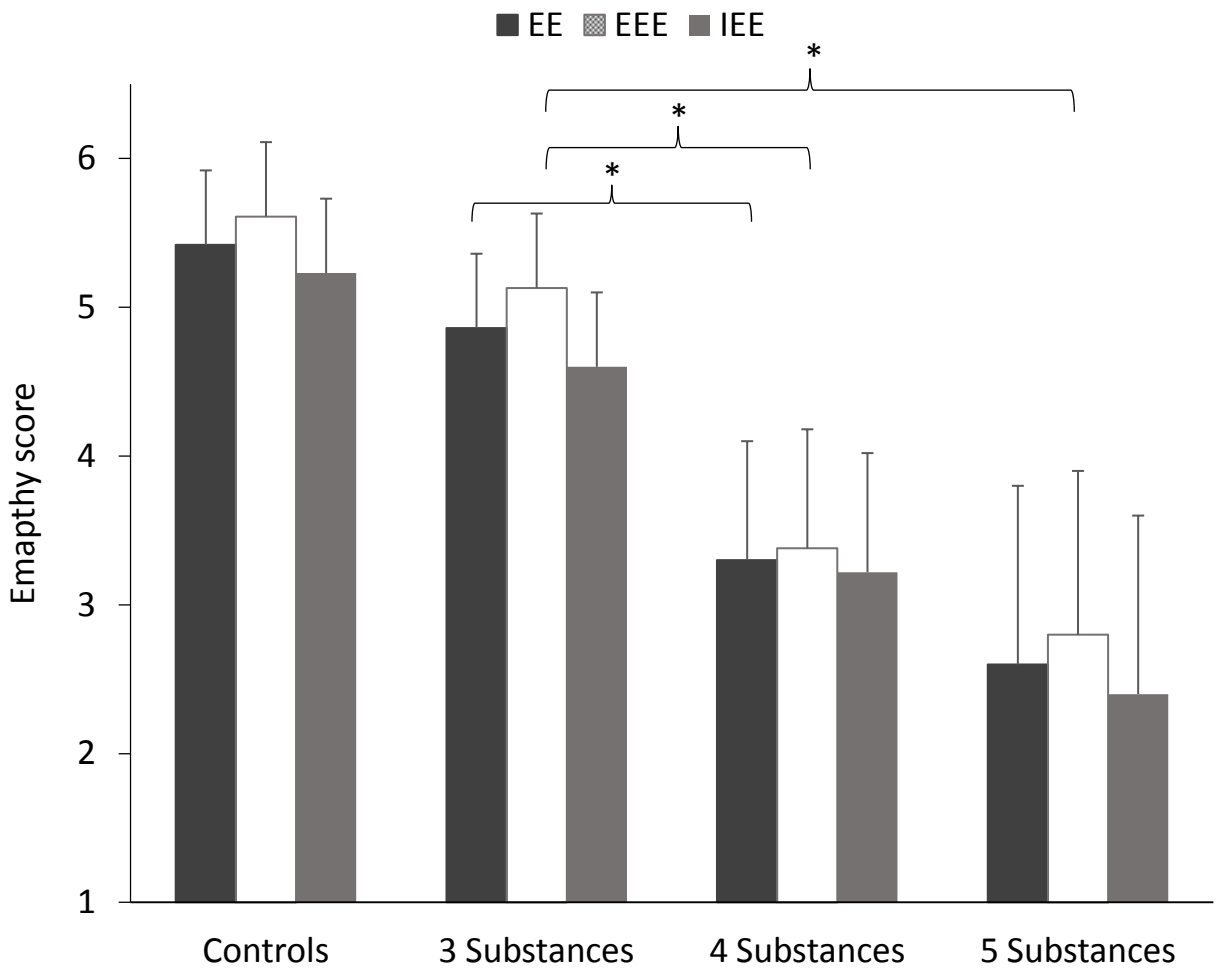

EE
EEE
IEE
Emapthy score
6
5
4
3
2
1
*
*
*
Controls
3 Substances
4 Substances
5 Substances

Figure Caption

Fig. 3. Distribution of substance use over all positive hair concentrations between PSU subgroups.

Note. MPH: methylphenidate.

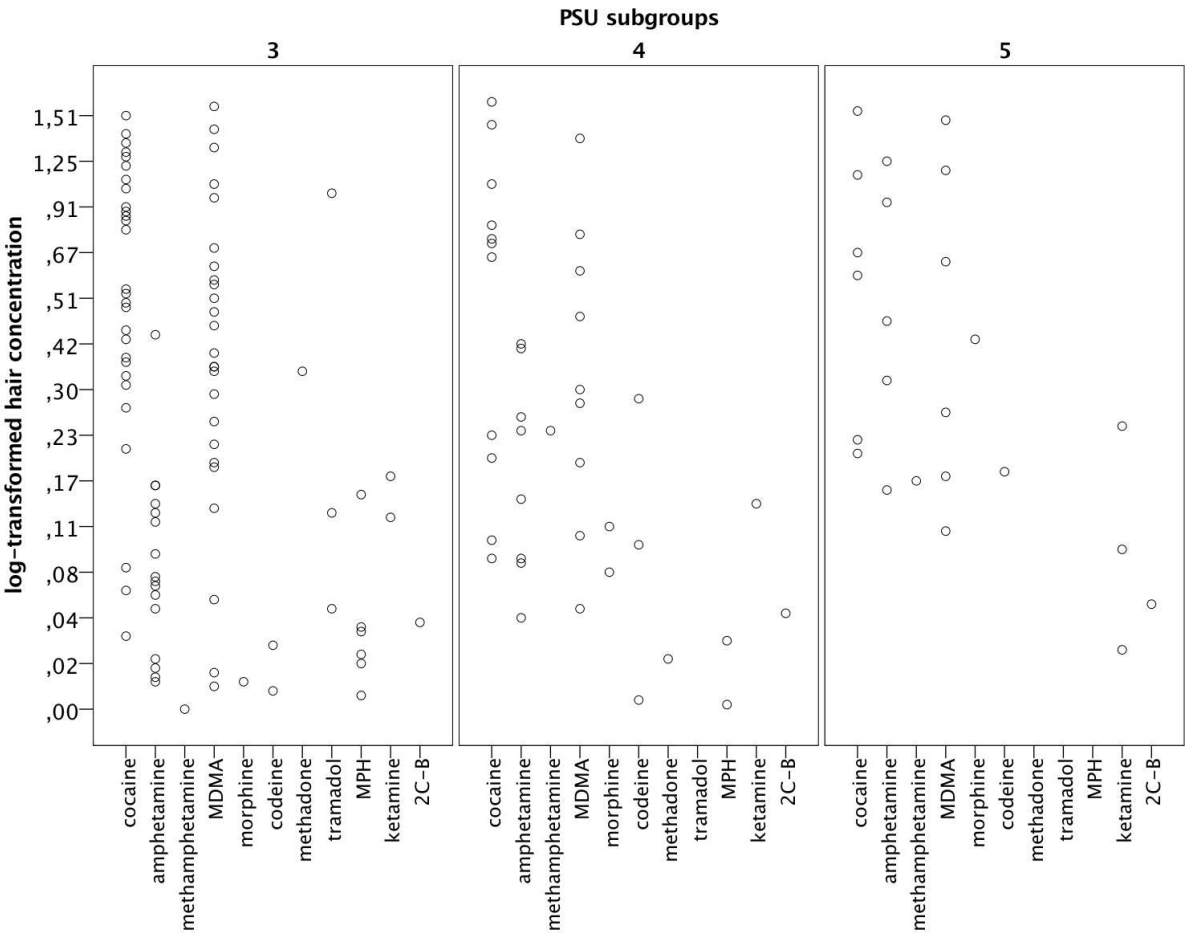
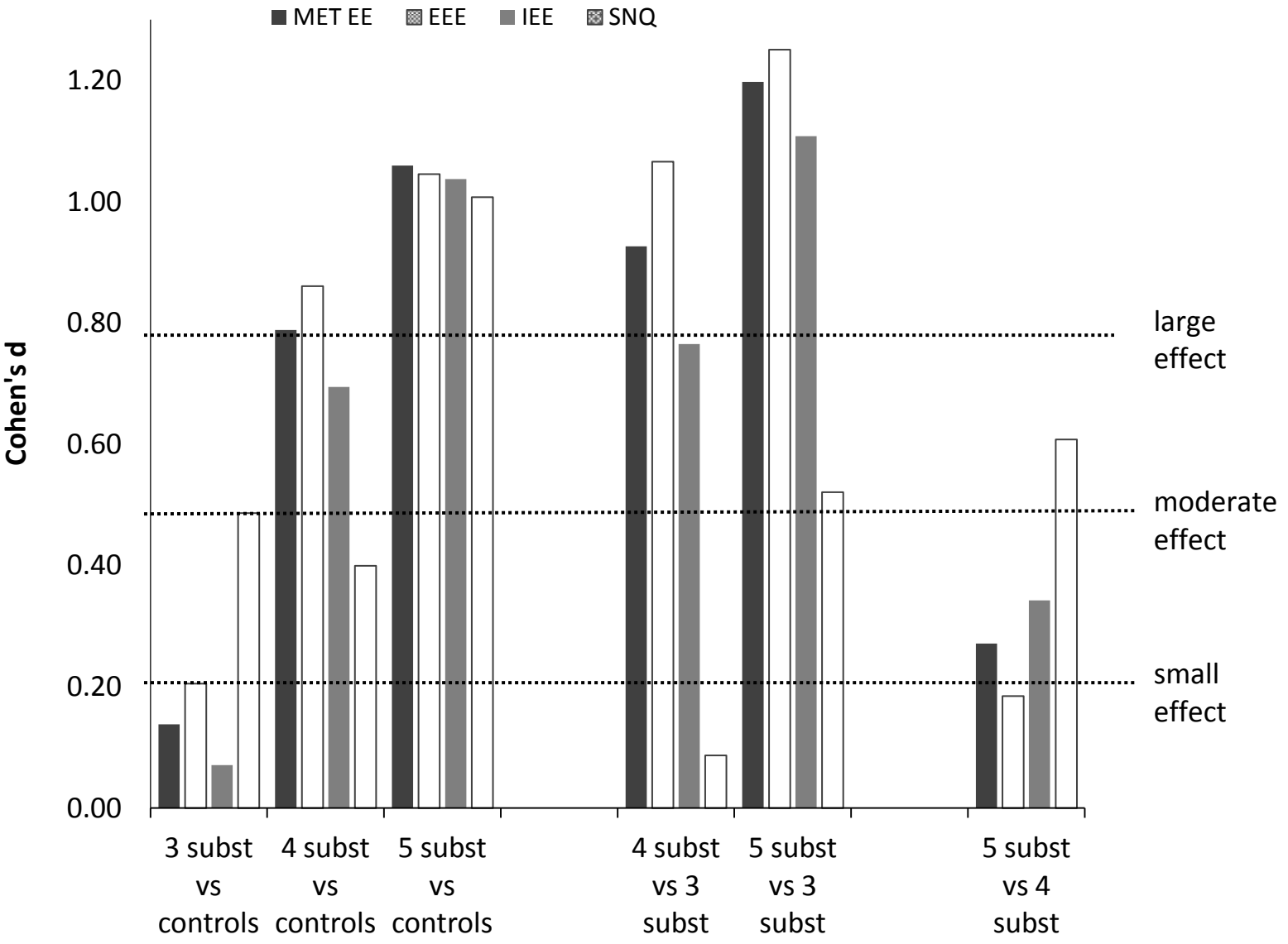

PSU subgroups
3
4
5
log-transformed hair concentration
1,51
1,25
,91
,67
,51
,42
,30
,23
,17
,11
,08
,04
,02
,00
cocaine
amphetamine
methamphetamine
MDMA
morphine
codeine
methadone
tramadol
MPH
ketamine
2C-B

Figure Caption

Fig. 4. Cohen's *d* effect sizes for comparisons between controls and PSU subgroups.

Note. EE: emotional empathy, EEE: explicit emotional empathy, IEE: implicit emotional empathy, SNQ: social network questionnaire, subst: substance


MET EE
EEE
IEE
SNQ
Cohen's d
1.20
1.00
0.80
0.60
0.40
0.20
0.00
large effect
moderate effect
small effect
3 subst vs controls
4 subst vs controls
5 subst vs controls
4 subst vs 3 subst
5 subst vs 3 subst
5 subst vs 4 subst

Supplement

Article title: *Socio-cognitive functioning in stimulant polysubstance users*

Authors: Sara L. Kroll; Michael D. Wunderli; Matthias Vonmoos; Lea M. Hulka; Katrin H. Preller; Oliver G. Bosch; Markus R. Baumgartner; Boris B. Quednow

Methods S1: Urine and hair toxicology

Urine toxicology analyses included following substances with cut-off values in parentheses (Substance Abuse and Mental Health Services Administration, 2012): amphetamine (<300ng/ml), benzodiazepine (<200ng/ml), tetrahydrocannabinol (<50ng/ml), cocaine (<150ng/ml), methadone (<300ng/ml), and opiate (<300ng/ml). These substances were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To objectively quantify substance use over the last six months, hair samples of 6m lengths were collected (if possible) and analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). Proximal hair segments with a length of up to six cm were analyzed. The following compounds were assessed: cocaine, amphetamine, methamphetamine, MDMA, methylphenidate, morphine, tramadol, methadone, codeine, ketamine, and ,5-dimethoxy-4-bromophenethylamine (2C-B).

For our routine protocol a three step washing procedure with water (2min shaking, 15ml), acetone (2min, 10ml) and finally hexane (2min, 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16h, ultrasonication) and in a second step with 3ml MeOH acidified with 50µl hydrochloric acid 33% (3h, ultrasonication). The extracts were dried and the residue reconstituted with 50µl MeOH and 500µl 0.2mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, morphine-d3, codeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5, methadone-d9, methylphenidate-d9, tramadol-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and

obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50psi); gas 2, nitrogen (60psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1mM formic acid (eluent B). The analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

Methods S2: Levels of substance use and PSUSI

With respect to the classification into low (1), medium (2), and severe substance use (3), hair samples of all recruited participants showing positive concentrations for the most consumed substances [i.e., cocaine (n=111), MDMA (n=78), and amphetamine (n=27)] were used to calculate separation values for three equal groups in relation to the group size. In order to be able to compare values of different hair samples, we normalized them by dividing substance hair-concentrations by their cut-off values (Cooper et al., 2012). The average of the normalized cut-off values in the three equal groups were used for the final classification into low (1), medium (2), and severe substance use (3) with respect of hair concentration

(Table S1). Levels of substance use (1 to 3) for each substance were summarized to the PSU severity index (PSUSI).

Table S1: Classification of low, medium and high substance use

a)

	Alcohol g/week women	Alcohol g/week men
Severity of substance use		
(1) low	< 147	< 287
(2) medium	147 - 286	287 - 426
(3) high	≥ 287	≥ 427

Note. Alcohol consumption levels defined by WHO, 2000

b)

	THC concentration ng/ml
Severity of substance use	
(1) low	50 - 87
(2) medium	88 - 102
(3) high	≥ 103

Note. Cut-off value by SAMHSA (Substance Abuse and Mental Health Services Administration, 2012)

c)

	Cocaine concentration ng/mg	**Cocaine norm (0.5)***	MDMA concentration ng/mg	**MDMA norm (0.2)***	Amphetamine concentration ng/mg	**Amphetamine norm (0.2)***	**Averaged norm values for substance use severity**
Severity of substance use							
(1) low	0.5 - 1.87	1 - 3.7	0.2 - 0.36	1 - 1.8	0.2 - 0.86	1 - 4.3	**1 - 3.3**[a]
(1) medium	1.88 - 6.62	3.8 - 13.2	0.37 - 0.74	1.9 - 3.7	0.87 - 3.54	4.4 - 17.7	**3.4 - 11.5**
(3) high	≥ 0.663	≥ 13.3	≥ 0.75	≥ 3.8	≥ 3.55	≥ 17.8	**≥ 11.6**

Note. * For normalization, hair concentrations were divided by their cut-off values reported in the literature (Cooper, 2012)

[a] Example: calculation of averaged normalized cut-off value for low (1) level: (3.7 + 1.8 + 4.3)/3 = 3.3

Table S2: Linear regression analyses for clinical and demographic variables predicting socio-cognitive functioning

a) MASC

	B	SE *B*	β	T-value	*p*
Constant	32.020	7.590		4.217	0.000
Sex	-0.415	1.385	-0.046	-0.300	0.766
Age	-0.199	0.083	-0.389	-2.392	**0.022**
YoE	-0.112	0.421	-0.041	-0.265	0.792
Verbal IQ	0.113	0.063	0.298	1.814	0.078
BDI sum score	-0.122	0.114	-0.215	-1.070	0.291
ADHD-SR	-0.058	0.082	-0.135	-0.709	0.483
Cluster B	-0.030	0.051	-0.098	-0.583	0.563

Note. Dependent variable: ToM sum score. Significant *p*-values are shown in bold.

R2 = 0.247 and F = 1.78, *p* = 0.120.

N = 47 individuals with PSU

The data met the assumption of independent errors (Durbin-Watson value = 1.62) and collinearity (tolerance values > 0.5 and VIF > 1 & < 10)

ADHD: Attention-deficit/hyperactivity disorder BDI: Beck's Depression Inventory, YoE: Years of education

b) EE

	B	SE *B*	β	T-value	*p*
Constant	3.561	2.732		1.303	0.200
Sex	-0.322	0.498	-0.108	-0.647	0.522
Age	0.030	0.030	0.178	1.011	0.318
YoE	0.183	0.152	0.204	1.209	0.234
Verbal IQ	-0.010	0.023	-0.082	-0.461	0.647
BDI sum score	-0.021	0.041	-0.109	-0.502	0.618
ADHD-SR	-0.025	0.030	-0.178	-0.862	0.394
Cluster B	0.017	0.018	0.172	0.948	0.349

Note. Dependent variable: EE score. Significant *p*-values are shown in bold.

R2 = 0.118 and F =.73, *p* = 0.651.

N = 47 individuals with PSU

The data met the assumption of independent errors (Durbin-Watson value = 2.04) and collinearity (tolerance values > 0.5 and VIF >1 & <10)

ADHD: Attention-deficit/hyperactivity disorder BDI: Beck's Depression Inventory, YoE: Years of education.

c) CES

	B	SE *B*	β	T-value	*p*
Constant	0.054	1.135		0.048	0.962
Sex	-0.324	0.207	-0.239	-1.564	0.126
Age	-0.019	0.012	-0.240	-1.493	0.144
YoE	-0.016	0.063	-0.040	-0.258	0.798
Verbal IQ	0.018	0.009	0.306	1.880	0.068
BDI sum score	-0.025	0.017	-0.291	-1.464	0.151
ADHD-SR	0.001	0.012	0.018	0.098	0.923
Cluster B	-0.014	0.008	-0.317	-1.908	0.064

Note. Dependent variable: CES z-score. Significant *p*-values are shown in bold.

R2 = 0.262 and F =1.93, *p* = 0.092.

N = 47 individuals with PSU

The data met the assumption of independent errors (Durbin-Watson value = 2.25) and collinearity (tolerance values > 0.5 and VIF > 1 & <10)

ADHD: Attention-deficit/hyperactivity disorder BDI: Beck's Depression Inventory, YoE: Years of education.

d) SNQ

	B	SE *B*	β	T-value	*p*
Constant	16.328	12.891		1.267	0.213
Sex	1.606	2.351	0.113	0.683	0.499
Age	-0.292	0.141	-0.359	-2.070	**0.045**
YoE	0.066	0.715	0.015	0.092	0.927
Verbal IQ	0.085	0.106	0.140	0.801	0.428
BDI sum score	-0.016	0.194	-0.018	-0.084	0.933
ADHD-SR	-0.069	0.139	-0.101	-0.497	0.622
Cluster B	-0.074	0.086	-0.154	-0.858	0.396

Note. Dependent variable: SNQ. Significant *p*-values are shown in bold.

R2 = 0.143 and F =.91, *p* = 0.512.

N = 47 individuals with PSU

The data met the assumption of independent errors (Durbin-Watson value = 2.00) and collinearity (tolerance values > 0.5 and VIF >1 & <10)

ADHD: Attention-deficit/hyperactivity disorder BDI: Beck's Depression Inventory, YoE: Years of education.

Table S3: Multiple linear regression analyses for substance-classes predicting socio-cognitive functioning within PSU (n=47)

Model 1

	B	SE *B*	β	T-value	*p*	R2 corr	*p* change in F
Step 1						-0.076	0.945
Constant	4.638	1.409		3.292	0.002		
Stimulants	0.056	1.118	0.008	0.050	0.960		
Empathogens	0.273	0.548	0.082	0.497	0.622		
THC	-0.236	0.489	-0.080	-0.482	0.632		
Alcohol	-0.123	0.479	-0.043	-0.256	0.799		
Step 2						0.100	**0.004**
Constant	6.396	1.412		4.529	<0.001		
Stimulants	0.854	1.055	0.122	0.809	0.423		
Empathogens	0.788	0.529	0.236	1.489	0.144		
THC	-0.089	0.449	-0.030	-0.198	0.844		
Alcohol	0.319	0.462	0.111	0.690	0.494		
Number of used substances	-0.929	0.306	-0.466	-3.040	**0.004**		
Step 3						0.098	0.347
Constant	5.981	1.479		4.043	<0.001		
Stimulants	1.149	1.101	0.164	1.044	0.303		
Empathogens	0.780	0.530	0.233	1.472	0.149		
THC	-0.061	0.451	-0.021	-0.135	0.893		
Alcohol	0.426	0.476	0.149	0.895	0.376		
Number of used substances	-1.231	0.441	-0.618	-2.791	**0.008**		
PSUSI	0.151	0.159	0.199	0.951	0.347		

Note. Dependent variable: EE. Significant *p*-values are shown in bold.

Step 1: R2=.017 and F=.19, *p*=.945.

Step 2: R2=.198 and F=2.03, *p*=.095.

Step 3: R2=.216 and F=1.83, *p*=.117.

The data met the assumption of independent errors (Durbin-Watson value = 2.54) and collinearity (tolerance values > 0.7 and VIF > 1 & < 10)

Model 2

	B	SE *B*	β	T-value	*p*	R2 corr	*p* change in F
Step 1						0.024	0.292
Constant	15.686	6.316		2.483	0.017		
Stimulants	-2.695	5.009	-0.082	-0.538	0.593		
Empathogens	1.566	2.457	0.100	0.637	0.527		
THC	4.555	2.190	0.329	2.080	**0.044**		
Alcohol	0.970	2.149	0.072	0.452	0.654		
Step 2						0.013	0.472
Constant	17.754	6.963		2.550	0.015		
Stimulants	-1.756	5.201	-0.053	-0.338	0.737		
Empathogens	2.172	2.609	0.138	0.833	0.410		
THC	4.727	2.215	0.341	2.134	**0.039**		
Alcohol	1.490	2.277	0.111	0.654	0.516		
Number of used substances	-1.093	1.507	-0.117	-0.725	0.472		
Step 3						-0.003	0.554
Constant	16.463	7.344		2.242	0.031		
Stimulants	-0.838	5.464	-0.025	-0.153	0.879		
Empathogens	2.148	2.630	0.136	0.817	0.419		
THC	4.814	2.234	0.347	2.151	**0.038**		
Alcohol	1.824	2.362	0.135	0.772	0.445		
Number of used substances	-2.035	2.190	-0.217	-0.929	0.358		
PSUSI	0.470	0.788	0.132	0.597	0.554		

Note. Dependent variable: SNQ. Significant *p*-values are shown in bold.

Step 1: R2=.109 and F=1.28, *p*=.292.

Step 2: R2=.120 and F=1.12, *p*=.364.

Step 3: R2=.128 and F=.98, *p*=.452.

The data met the assumption of independent errors (Durbin-Watson value = 2.27) and collinearity (tolerance values > 0.7 and VIF > 1 & < 10)

Figure S1a: Distribution of alcohol use between PSU subgroups

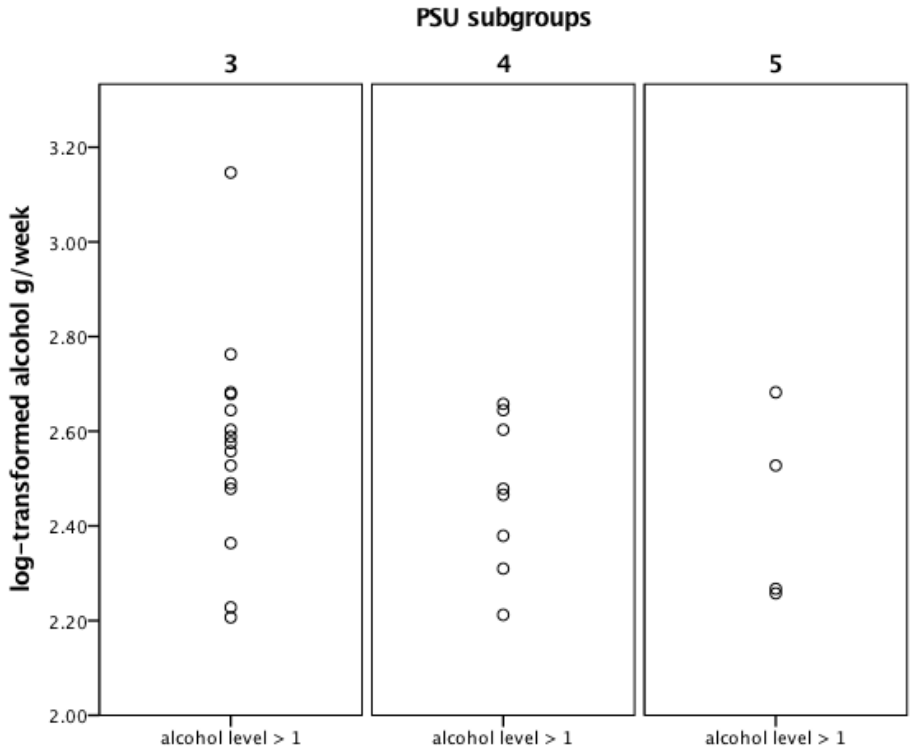
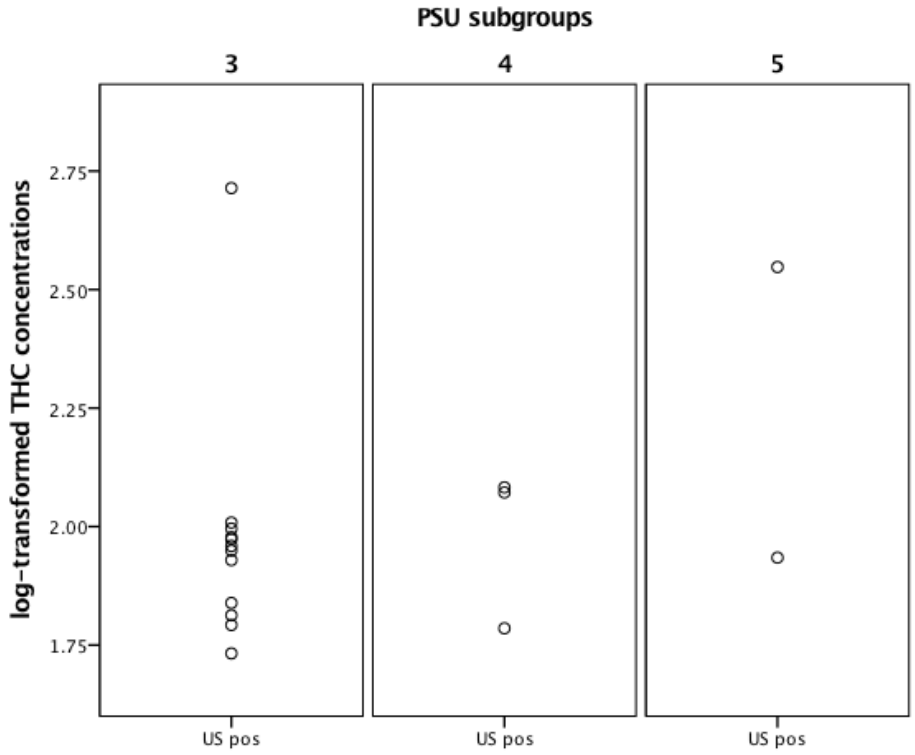


Figure S1b: Distribution of THC over all positive US between PSU subgroups



Note. US: urine sample

References

Cooper, G.A., Kronstrand, R., Kintz, P., Society of Hair, T., 2012. Society of Hair Testing guidelines for drug testing in hair. Forensic Sci Int 218(1-3), 20-24.
Substance Abuse and Mental Health Services Administration, 2012. Clinical Drug Testing in Primary Care. Substance Abuse and Mental Health Services Administration, Rockville, MD.